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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/649,480 | 08/27/2003 | Thomas J. Stegmann | CVGENG.008CP1 | 5376 |

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| EXAMINER | |
|---|---|
| LI, BAO Q | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/649,480 | STEGMANN ET AL. | |
| | Examiner | Art Unit | |
| | Bao Qun Li | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,12,16-34,36 and 37* is/are pending in the application.

4a) Of the above claim(s) *16,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1,12, 17, 20-34, 36 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### RCE

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission and amendment filed on 05/18/2006 have been entered and RCE follow:

### *Response to Amendment*

This is a response to the amendment filed on 05/18/06. Claim 1 has been amended. New claim 37 has been added. Claims 2-11, 13-15 and 35 have been canceled. Claims 16, 18-19 are withdrawn from the consideration. Claims 1, 12, 17, 20-34 and 36-37 in the scope of SEQ ID NO: 6 and SEQ ID NO: 7 are pending and considered before the examiner.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### *Priority*

1. The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

2. The disclosure of the prior-filed application, Application No. 09/358/780 and 60/093,962, fails to provide adequate support or enablement of claims 12, 17 and 37 in the manner provided by the first paragraph of 35 U.S.C. 112.

3. The disclosure of the prior-filed application, Application No. 09/929/945, filed on August 15, 2001 and provision application SN. 60,225,406 filed on August 15, 2000 fails to provide adequate support or enablement of claims 1, 12, 16-34 and 36-37 in the manner provided by the first paragraph of 35 U.S.C. 112. Claim

4. Accordingly, the effective filing date of claims 12, 17 and 37 is considered to be the filing date of current application August 27, 2003. The effective filing date of claims 1, 20-34 and 36 are considered to be July 24, 1998.

### *Declarations*

5. The **Declarations** by Dr. Stegmann under 37 CFR 1.131 and 1.132 filed on August 25, 2005, has been acknowledged. However, the declarations are insufficient to overcome the rejection over claims 12, 17 and 37, because the effective filling date of claims 12, 17 and 37 is considered to be August 27, 2003, and the primary reference by Schumacher et al. (Circulation, Feb, 1998, Vol. 97, pp. 645-650) is published more then one year of the effective filling date of said claims. The rejections over claims 12, 17 and 37 is on a statutory bar under 35 U.S.C. 102(b) and thus cannot be overcome by an affidavit or declarations under 37 CFR 1.131 and 37 CFR 1.132..

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 12, 17 and 37 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Htun et al. (J. Mol. Cell. Cardiol. April 1998, Vol. 30, pp. 867-877), Linemeyer et al (US patent NO. 5,401832A) and Kordyum et al. (US Patent No. 6,773,899B2).

8. In response to the previous Office action, applicant amended claim 1 and also filed Declarations under 37 CFR 1.131 and 1.132. Applicants assert that the rejection should be withdrawn in view of the amendment and Declarations.

9. Applicants' argument has been fully considered; the rejection over claims 1, 20-34 and 36 are withdrawn in view of the Declarations. However, the rejection over claims 12, 17 and 37 cannot withdrawn because the effective filling date of claims 12, 17 and 37 is considered to be August 27, 2003, and the primary reference by Htun et al. is published more then one year of the effective filling date of said claims.

10. To this context, the rejection over claims 12, 17 and 37 are still maintained.

11. Claims 1, 12, 17, 23-27, 34 and 36 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Fasol et al. (J. Thorac Cardiovasc. Surg. 1994, Vol. 107, pp. 1432-1439).), Linemeyer et al (US patent NO. 5,401832A) and Kordyum et al. (US Patent No. 6,773,899B2).

12. Claims 12, 17, 23-27, 34 and 36 are directed to a method for revascularizing an ischemic region comprising preparing a composition comprising a recombinant fibroblast growth factor –1 (FGF-1), fibrin glue and anticoagulant, and injecting it into the ischemic myocardium region, wherein said FGF-1 comprises the amino acid sequence of SEQ ID NO: 7 from position 2 to position 141 or is encoded by a gene comprising the sequence of SEQ ID NO: 6.

13. Applicants traverse the rejection and assert that the reference by Fasol et al. differs from the presently claimed claims after amendment, because Fasol. et al. only teach to implant a fibrin glue in non-ischemic tissue, rather then injection into an ischemic region of the myocardium or injection directly into the myocardium. Therefore, the reference by Fasol. et al. neither teaches nor suggests the claimed invention.

14. Applicants' argument has been respectfully considered; however, it is not found persuasive because the reference by Fasol. et al. teaches the same method steps about the claimed method about including to apply a composition comprising FGF directly into the myocardium in order to help regeneration of new blood vessels in said myocardium tissue as the claimed method drafted. For example, Fasol. et al. teach a similar surgical

open hear surgery procedure comprising to make a thoracotomy incision, access to the myocardium of the left ventricle via a small incision into the pericardium, and place the composition to the left ventricular myocardium. They found that the administration of the composition comprising FGF to said myocardial tissue induces a significant blood vessel growth, and an addition of fibrin glue in the composition meets makes it easily for applying the angiogenesis growth factor to the target organ etc as previous office addressed (See pages 2-3, 4-5, Fig. 4, pages 7-10). In particular, Fasol et al. teaches to inject 0.5 ml of fibrin glue containing 1 μg of α-ECGF (Synonymies of FGF) directly into the myocardium of the experimental animal by syringe (See SECTION OF Surgical procedure, especially in Fig. 1), wherein said α-ECGF is expressed by a recombinant DNA technique (See the 1st paragraph in section of MATERIALS AND METHODS).

15. Fasol. et al. also suggests the claimed invention, because Fasol. et al. clearly indicates in the reference that the ischemic tissue injury is a pathogenic condition of heart. During such a myocardial pathological condition, the myocardial tissue secrets the endogenous growth factors including (α and β ECGF) to stimulate the angiogenesis and growth of preexisting collateral vessels. However, the revascularization under such myocardium condition does not proceed fast enough to meet the body requirement, and it is often inadequate to prevent clinical manifestation of ischemic disease. Therefore, their investigation demonstrate that enhancement angiogenesis and growth of collaterals and salvage of infracted myocardium can be made by in vivo administrating a composition comprising the exogenous angiogenic growth factor, FGF and fibrin glue. They suggests that their method meets the requirement of such conditions and has an additional advantage of a clinical applicability (Se the section of Discussion).

16. Regarding the argument that applicants assert that Fasol et al. do not teach to injection of FGF directly to the ischemic region, applicants are reminded that although Fasol et al. do not teach to inject FGF into the ischemic area, it does not teach that the composition should not be avoid injecting into the ischemic region. More importantly, the reason for not injecting into the ischemic region is that Fasol et al. need to see the separate angiogenesis effect produced by a directly injection of an exogenous FGF into the myocardial tissue. Therefore, the reference by Fasol. et al. does not teach away from

the claimed invention. In fact, the reference by Fasol. et al. teach both the endogenous and exogenous FGF exhibit the same and synergistic angiogenetic biological effect toward stimulating blood vessel growth during the myocardium tissue infarction. It does not teach that ischemic injection of FGF should not used.

17. Since there is no unexpected result presented by applicants, the claimed invention as a whole is still considered prima facie obvious absence unexpected results.

**New Grounds of rejections:**

***Claim Rejections - 35 USC § 102***

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

19. Claims 1 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Ellis et al. (US Patent No. 6,045,565A).

20. Ellis et al. teach a method for treating revascularization of ischemic myocardial myocardium comprising directly injecting a composition comprising an angiogenesis material carried by an adhesive material into the myocardium tissue that requires to increase blood circulation via a directly needle injection, and the angiogenesis substance is to stimulate the blood vessel growth and the adhesive material is absorbed into the myocardium in order to let said angiogenetic material absorbed by the myocardial tissue . Hereby, the new blood vessels growth is prompted by both the healing response to the

wound and by the angiogenesis material provided. Ellis et al. teach that said angiogenesis materials include VEGF and FGFs, and said adhesive materials include fibrin glues. Ellis et al. also teach that an alternative method utilizes an angiogenic material injected into the myocardium from the exterior of the hear, in conjunction with an open heart surgery or during a minimally invasive procedure (Please see columns 1-2 and claims 1-9). Therefore, the claimed invention is anticipated by the cited reference.

***Claim Rejections - 35 USC § 103***

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 12, 17 and 37 are rejected under 35 U.S.C. 103(a) under the same ground as stated in the previous Office Action, as being unpatentable over Schumacher et al. (Circulation, Feb, 1998, Vol. 97, pp. 645-650), Kordyum et al. (US Patent No. 6,773,899B2) and Linemeyer et al (US patent NO. 5,401832A).

23. In response to the previous Office action, applicant amended claim 1 and also filed Declarations under 37 CFR 1.131 and 1.132. Applicants assert that the rejection should be withdrawn in view of the amendment and Declarations.

24. Applicants' argument has been fully considered; the rejection over claims 1, 20-34 and 36 are withdrawn in view of the Declarations. However, the rejection over claims 12, 17 and 37 cannot withdrawn because the effective filling date of claims 12, 17, and 37is considered to be August 27, 2003, and the primary reference by Schumacher et al. (Circulation, Feb, 1998, Vol. 97, pp. 645-650) is published more then one year of the effective filling date of said claims.

25. To this context, Schumacher et al. disclose a method for induction of neoangiogenesis in ischemic myocardium by human acidic growth factor (FGF-1) comprising preparation of pharmaceutical composition comprising a human FGF-1

expressed by apathogenic strain E Coli that carries a plasmid encoding the genetic information of human FGF-1, and injection of the composition directly into the myocardium distal to the internal mammary artery (IMA) and left anterior descending coronary artery (LAD) anastomosis and close to the LAD, during the open heart venous bypass surgery at the concentration about 10 μg/kg body weight. They have demonstrated that the administration of the human FGF-1 into the ischemic myocardium region induce the significantly revascularization of the blood vessel in compared with the negative control. They concluded that neoangiogenesis induced by human FGF-1 open s up new possibilities for treatment of ischemic myocardial disease (See entire document, especially, see pages 645- 646, Figs. 4-8 and page 650). Schumacher et al. does not teach the nucleic acid and amino acid sequence of human FGF-1.

26. Linemyer et al. disclose the exactly same human FGF-1 polypeptide sequence, wherein the amino acid residues of said polypeptide has 100% identical to the amino acid residues of 2-141 of the claimed human FGF-1 of claim 7 and amino acid sequences as claimed drafted (In fact, HECGF is an synonym of FGF). In addition, Linemyer et al. teaches that the said recombinant Human FGF-1 is used for promoting cell growth, healing and revascularization of grafted blood vessel (See Table 1 and abstract).

27. Kordyum et al. disclose the exactly nucleic acid sequence (SEQ ID NO: 6 and its deduced amino acid sequence that is 100% identical to the claimed nucleic acid sequence of SEQ ID NO: 6 and amino acid sequence of claimed SEQ IFD N0: 7, Moreover, Kordyum et al. disclose that said nucleic acid sequence encodes the polypeptide such as ECGF (Previous name of FGFII) having a similar function as a native isolated human FGF-I having a potential for the treatment of the damaged or regeneration of blood vessel or endothelial cell-line tissues (See SEQ ID NO: 6 and column 14, example 6).

28. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and to treat myocardium ischemic infarction by combining the teachings by all cited references above absence of unexpected result. Hence the claimed invention as a whole is prima facie obvious absence unexpected results.

29. Claims 1, 12, 17 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. (US Patent No. 6,045,565A) in view of Kordyum et al. (US Patent No. 6,773,899B2) and Linemeyer et al (US patent NO. 5,401832A).

30. Ellis et al. teach a method for treating revascularization of ischemic myocardial myocardium comprising directly injecting a composition comprising an angiogenesis material carried by an adhesive material into the myocardium tissue that requires to increase blood circulation via a directly needle injection, and the angiogenesis substance is to stimulate the blood vessel growth and the adhesive material is absorbed into the myocardium in order to let said angiogenetic material absorbed by the myocardial tissue . Hereby, the new blood vessels growth is prompted by both the healing response to the wound and by the angiogenesis material provided. Ellis et al. teach that said angiogenesis materials include VEGF and FGFs, and said adhesive materials include fibrin glues. Ellis et al. also teach that an alternative method utilizes an angiogenic material injected into the myocardium from the exterior of the hear, in conjunction with an open heart surgery or during a minimally invasive procedure (Please see columns 1-2 and claims 1-9). Ellis et al. do not particular teach the amino cid sequence of a FGF peptide like SEQ ID NO. 7 or its fragment and a DNA sequence encoding a FGF peptide like SEQ ID NO: 6.

31. Linemyer et al. disclose the exactly same human FGF-1 polypeptide sequence, wherein the amino acid residues of said polypeptide has 100% identical to the amino acid residues of 2-141 of the claimed human FGF-1 of claim 7 and amino acid sequences as claimed drafted (In fact, HECGF is an synonym of FGF). In addition, Linemyer et al. teaches that the said recombinant Human FGF-1 is used for promoting cell growth, healing and revascularization of grafted blood vessel (See Table 1 and abstract).

32. Kordyum et al. disclose the exactly nucleic acid sequence (SEQ ID NO: 6 and its deduced amino acid sequence that is 100% identical to the claimed nucleic acid sequence of SEQ ID NO: 6 and amino acid sequence of claimed SEQ IFD N0: 7, Moreover, Kordyum et al. disclose that said nucleic acid sequence encodes the polypeptide such as ECGF (Previous name of FGFII) having a similar function as a native isolated human FGF-I having a potential for the treatment of the damaged or regeneration of blood vessel or endothelial cell-line tissues (See SEQ ID NO: 6 and column 14, example 6).

33. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and to treat myocardium ischemic infarction by combining the teachings by all cited references above absence of unexpected result. Hence the claimed invention as a whole is prima facie obvious absence unexpected results.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 6:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BAOQUN LI, MD
PATENT EXAMINER

Bao Qun Li